2. CANCER-PREVENTIVE EFFECTS IN HUMANS

2.1 Methodological considerations

Randomized trials addressing body fatness and risk of cancer are rare and are often not feasible. Hence, observational epidemiological studies on various weight parameters are relied on to provide evidence. Body fatness can be a reflection of genetic, metabolic, lifestyle, dietary, environmental, and psychosocial factors. Therefore, it is important that epidemiological studies are designed appropriately to control for the many potential confounders. This section reviews some of the methodological issues in epidemiological studies that must be carefully considered when evaluating the body of evidence on the association between body fatness and risk of cancer.

2.1.1 Bias

(a) Recall bias

Retrospective studies addressing body fatness and risk of cancer may rely on participants' recollections of their past weight or other measures. If there is differential recall between cases and controls, or between overweight people and lean people, this is considered recall bias. This imbalance can have an impact on estimates of effect, particularly in case–control studies.

(b) Selection bias

Non-randomized studies are at risk of selection bias, because subjects are not allocated to groups at random, and instead are generally selected based on their disease or exposure status. Therefore, if cases and controls, or exposed and unexposed individuals, are selected systematically in a different way, estimation of the association between exposure and risk can be affected, depending on the study design.

For example, in case–control studies, those who agree to participate as controls may be more likely to have a history of being at a healthy weight, and may be more likely to engage in other healthy behaviours, than those who do not agree to participate. They may not be representative of the larger population from which they are selected, and this can result in an overestimation or underestimation of the association between body fatness and risk of cancer.

(c) Detection bias

Detection bias refers to systematic differences between groups in the detection of outcomes of interest. Studies of cancers that can be detected by screening are at higher risk of this bias, affecting their estimate of effect. Individuals who are likely to engage in healthy behaviours, such as behaviours that lead to maintaining a healthy weight, may also be more likely to seek the recommended screening tests. They may

therefore be more likely to receive early diagnosis and to have access to early treatment, which can affect their prognosis. If the outcome of interest is mortality, individuals who receive early diagnosis may be less likely to die from the disease, because of earlier treatment. If these individuals are also more likely to have a lower weight, this could result in an overestimation of the impact of these behaviours.

Similarly, individuals who are less likely to engage in healthy behaviours, and may be less likely to be at a healthy weight, may also be less likely to participate in screening and therefore will be less likely to receive early diagnosis and to have access to early treatment. The estimated effect of body fatness on the poorer outcomes in such individuals can be affected by their behaviour. This type of bias is of less concern for cancers that are more likely to be fatal, because early detection or screening may not have as large an effect if the outcome of interest is death.

2.1.2 Confounding

Confounding is the result of an association between exposures, resulting in the conclusion that the effect on the risk of disease is due to one variable rather than another. Although the exposure and the risk of disease are linked, this is due to their joint relationship with the confounding variable, rather than due to a direct relationship.

Potential confounders can be addressed either in the design of studies or in the analysis of the data. In case–control studies, suspected confounders can be controlled for by matching on those variables. Similarly, in cohort studies, unexposed and exposed groups can be selected to be as similar as possible with respect to the potential confounders. In the analysis of the data, stratification or statistical adjustment can be used to control for potential confounders.

Individuals who maintain a healthy weight may be more likely to engage in other healthy behaviours, so these associations should be explored as potential confounders when investigating the association of body fatness with risk of cancer. In high-income countries, people with lower socioeconomic status are more likely to be overweight or obese. Race and other factors may also be related to body fatness and to risk of cancer, and when the results of epidemiological studies are evaluated, it is important to consider whether such confounders have been adjusted for appropriately.

Tobacco use is strongly associated with a higher risk of many cancers. However, smoking is more common among lean individuals than among overweight or obese individuals; one mechanism that could explain this association is that smoking can have an anorectic effect. Smoking must therefore be properly adjusted for to ensure that it is not confounding the relationship between body fatness and risk of cancer. Current smoking modifies weight gain trajectory; therefore, among former smokers, time since quitting must be considered when stratifying by smoking status.

2.1.3 Reverse causation

Reverse causation occurs when the exposure is affected by the outcome, whereas it is usually assumed that the outcome is affected by the exposure. The direction of causality must be considered when evaluating associations between body fatness and risk of cancer. Weight may affect risk of cancer, but preclinical cancer can also cause weight loss. Additional chronic diseases that may affect risk of cancer may also result in weight loss. The timing of measurement must also be considered, because closer to the time of diagnosis, body fatness is more likely to be affected by disease.

2.1.4 Mendelian randomization

In the absence of large-scale and long-term randomized controlled trials (RCTs) on body fatness and risk of cancer, the concept of Mendelian randomization can provide insights into whether observed associations are causal, by leveraging the properties of genetic variation to overcome limitations present in observational epidemiological studies. Mendelian randomization exploits the random allocation of alleles between parents and offspring at conception as the basis of natural experiment to strengthen causal inference within the association between a modifiable exposure and an outcome of interest (Smith & Ebrahim, 2003, 2004; Lawlor et al., 2008).

The method relies on three main assumptions: the genetic variant (i) is a valid instrument, in that it is reliably associated with the exposure of interest, (ii) is not independently associated with the outcome, except through the exposure (known as the exclusion restriction criterion), and (iii) is not associated with any of the confounding factors that would otherwise distort the observational association between the exposure and the outcome. There are several general limitations to this methodology (for reviews, see Smith & Ebrahim, 2003, 2004). Importantly, effects of common genetic variants on the exposure are small and prone to weak instrumentation if used alone, which can bias estimates (Smith & Ebrahim, 2003, 2004). Therefore, using a greater number of variants included within Mendelian randomization analyses increases the variance explained in a given trait and can thus improve the precision of the causal estimate (Locke et al., 2015).

References

Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G (2008). Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*, 27(8):1133–63. doi:10.1002/sim.3034 PMID:17886233

Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al.; LifeLines Cohort Study; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium (2015). Genetic studies of body mass index yield new insights for obesity biology. *Nature*, 518(7538):197–206. doi:10.1038/nature14177 PMID:25673413

Smith GD, Ebrahim S (2003). 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*, 32(1):1–22. doi:10.1093/ije/dyg070 PMID:12689998

Smith GD, Ebrahim S (2004). Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol*, 33(1):30–42. doi:10.1093/ije/dyh132 PMID:15075143